Enamine Chemistry. Part XIV.[1] Reaction of αβ-Unsaturated Acid Chlorides with Tertiary Enamino-ketones and -esters

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4-Acetyl- and 4-benzoyl-3-(substituted amino)cyclohex-2-en-1-ones have been isolated from the reaction of acryloyl chloride with tertiary enamino-ketones. Tertiary enamino-ethyl esters give the corresponding 4-ethoxy-carbonylcyclohexenones. 2',4'-Dimethyl-6'-morpholinoaq⌐ᵗᵧᵖhenone has been obtained from the self-condensation of 4-morpholinopent-3-en-2-one and identified from ᵗ ⌐ₓtral data.

RECENTLY we have shown that the reactions of αβ-unsaturated acid chlorides with primary and secondary enamino-ketones,[1] enamino-esters,[1] and imines,[2] give tetrahydro-2-oxopyridines or octahydro-2-oxoquinolines. We now report that the reactions of acryloyl chloride and methacryloyl chloride with tertiary enamino-ketones and -esters (I) (Table 1) give cyclohex-2-en-1-ones (II). Preparative and spectral data are summarised in Table 2.

that of the double-bond isomer (III) can be attributed to reduced mesomeric stabilisation of the enamino-ketone system in (III): steric interactions between the R^1_2N and COR^2 groups in (III) would result in twisting of these groups out of the plane of the carbon–carbon double bond. Cyclohexenones were not obtained from the corresponding reactions with cinnamoyl chloride and crotonoyl chloride; unchanged starting materials and

TABLE 1

Tertiary enamino-ketones and -esters (I): synthesis and spectra

| Compound [a] | | Yield (%) | M.p. or b.p. (°C) | Found (%) | | | Required (%) | | | M^+ | $\nu_{max.}/$ cm⁻¹ | τ (CDCl₃) |
R¹₂N	R²			C	H	N	C	H	N			
M	OEt	46	124—128 at 1 mmHg [c]	60.35	8.5	6.9	60.3	8.5	7.0	199	1687[b] 1587	5.15 (s, =CH), 5.86 (q, CH₂·CH₃), 6.23 (m, CH₂·O·CH₂), 6.73 (m, CH₂·N·CH₂), 7.58 (s, =CMe), 8.75 (t, CH₂·CH₃)
Py	OEt	67	126 at 1 mmHg	65.85	9.1	7.4	65.6	9.3	7.65	183	1678[b] 1575	5.48 (s, =CH), 5.88 (q, CH₂·CH₃), 6.65 (m, CH₂·N·CH₂), 7.49 (s, =CMe), 8.06 (m, [CH₂]₂), 8.73 (t, CH₂·CH₃)
P	OEt	70.5	122 at 0.6 mmHg	66.8	9.4	7.4	67.0	9.65	7.1	197	1683[b] 1580	5.27 (s, =CH), 5.94 (q, CH₂·CH₃), 6.72 (m, CH₂·N·CH₂), 7.59 (s, =CMe), 8.45 (m, [CH₂]₃), 8.77 (t, CH₂·CH₃)
M	Me	61	46—47 (from hexane)	64.2	9.2	8.1	63.9	8.9	8.3	169	1643[d] 1548	4.76 (s, =CH), 6.25 (m, CH₂·O·CH₂), 6.67 (m, CH₂·N·CH₂), 7.54 (s, =CMe), 7.92 (s, COMe)
Py	Me	77	114—116 [e] (from hexane)	70.4	10.1	9.2	70.6	9.8	9.15	153	1620[d] 1533	5.05 (s, =CH), 6.65 (m, CH₂·N·CH₂), 7.48 (s, =CMe), 7.98 (s, COMe), 8.07 (m, [CH₂]₂)
P	Me	61	47—48 (from hexane)	71.5	10.0	8.1	71.9	10.2	8.4	167	1615[d] 1530	4.77 (s, =CH), 6.65 (m, CH₂·N·CH₂), 7.51 (s, =CMe), 7.94 (s, COMe), 8.36 (m, [CH₂]₃)
M	Ph	74	142—144 (from petrol–benzene)	72.9	7.5	5.9	72.7	7.4	6.1	231	1605[d] 1573 1530	2.16 and 2.61 (m, Ph), 4.13 (s, =CH), 6.27 (m, CH₂·O·CH₂), 6.61 (m, CH₂·N·CH₂), 7.41 (s, =CMe)
Py	Ph	79	165—166 (from petrol–benzene)	78.3	8.2	6.4	78.1	7.9	6.5	215	1598[d] 1593 1524	2.16 and 2.64 (m, Ph), 4.43 (s, =CH), 6.64 (m, CH₂·N·CH₂), 7.38 (s, =CMe), 8.08 (m, [CH₂]₂)
P	Ph	71.5	94—96 (from hexane–benzene)	78.6	8.8	6.0	78.6	8.3	6.1	229	1613[d] 1570 1530	2.16 and 2.62 (m, Ph), 4.16 (s, =CH), 6.57 (m, CH₂·N·CH₂), 7.37 (s, =CMe), 8.36 (m, [CH₂]₃)

[a] M = Morpholino, Py = pyrrolidino, P = piperidino. [b] Liquid film. [c] Lit., b.p. 120—124° at 0·5 mmHg (J. F. Tinker and T. E. Whatmough, *J. Amer. Chem. Soc.*, 1952, **74**, 5235). [d] Nujol. [e] Lit., m.p. 115—116° (N. J. Leonard and J. A. Adamick, *J. Amer. Chem. Soc.*, 1959, **81**, 595).

No attempt has been made to obtain optimum yields but, as expected from previous investigations,[2] the best conditions involve (a) the use of dilute solutions and (b) slow addition of the acid chloride to the enamine solution in boiling benzene [method (B)]. The isomeric structures (III)—(V) are ruled out by the presence of an olefinic singlet in the n.m.r. spectrum of each of the products. The preference for structure (II) rather than

the amides (VI) were the only compounds isolated in a sufficiently pure state for identification.

In the case of the reaction between acryloyl chloride and 4-morpholinopent-3-en-2-one a second product, derived by self-condensation of two molecules of the enamine, was also isolated. This has been identified as 2',4'-dimethyl-6'-morpholinoacetophenone (VII) from analytical and spectral data. The u.v. spectrum

[1] Part XIII, P. W. Hickmott and G. Sheppard, *J. Chem. Soc.* (C), 1971, 2112.

[2] P. W. Hickmott and G. Sheppard, *J. Chem. Soc.* (C), 1971, 1358.

[$\lambda_{max.}$ (MeOH) 238 nm (ϵ 7900)] is indicative of a non-planar chromophoric system, typical of a 2',6'-dialkyl-acetophenone [3a] rather than an *ortho-* or *para-*dialkyl-aminoacetophenone.[3b] Although the [1]H n.m.r. spectrum of a solution in perdeuteriobenzene showed a singlet at

then obtained, thus allowing structural confirmation to be obtained by utilisation of the nuclear Overhauser effect. Irradiation at the frequency of the signals due to the methylene protons α to the nitrogen atom of the morpholine ring (at τ 7·11) resulted in a 13% increase in

TABLE 2

Cyclohex-2-en-1-ones (II): synthesis and spectra

Compound [a]				Yield (%)	M.p. (°C)	Found (%)			Required (%)			M^+	$v_{max.}/$ cm⁻¹	$\lambda_{max.}$ (MeOH)/ nm (ϵ)	τ (CDCl₃)
$R^1{}_2N$	R^2	R^3	Method			C	H	N	C	H	N				
M	OEt	H	A	27	75	62·1	7·7	5·6	61·7	7·5	5·5	253	1725 [b]	303	4·62 (s, =CH), 5·70 (q, $CH_2 \cdot CH_3$),
			B	44	(from								1620	(28,200)	6·22 (m, CH and $CH_2 \cdot O \cdot CH_2$),
			C	40	petrol–								1571		6·62 (m, $CH_2 \cdot N \cdot CH_2$), 7·62 (s,
					benzene)										$[CH_2]_2$), 8·69 (t, $CH_2 \cdot CH_3$)
Py	OEt	H	A	33	Oil	65·9	8·0	5·7	65·8	8·0	5·9	237	1727 [c]	304	4·91 (s, =CH), 5·76 (q, $CH_2 \cdot CH_3$),
													1612	(28,900)	6·61 (m, CH and $CH_2 \cdot N \cdot CH_2$),
													1560		7·67 (s, $[CH_2]_2$), 8·02 (m,
															$[CH_2]_2$), 8·72 (t, $CH_2 \cdot CH_3$)
P	OEt	H	C	35	Oil	66·7	8·0	5·3	66·9	8·4	5·6	251	1725 [c]	307	4·67 (s, =CH), 5·78 (q, $CH_2 \cdot CH_3$),
													1615	(30,000)	6·38 (m, CH), 6·68 (m, $CH_2 \cdot$
													1555		$N \cdot CH_2$), 7·68 (s, $[CH_2]_2$), 8·36
															(m, $[CH_2]_3$), 8·72 (t, $CH_2 \cdot CH_3$)
M	OEt	Me	B	11·5	Oil	62·8	7·7	5·0	62·9	7·9	5·2	267	1723 [c]	302	4·69 (s, =CH), 5·76 (q, $CH_2 \cdot CH_3$),
													1620br	(23,450)	6·26 (m, CH and $CH_2 \cdot O \cdot CH_2$),
													1563br		6·67 (m, $CH_2 \cdot N \cdot CH_2$), 7·4—8·2
															(complex, $CH_2 \cdot CH$), 8·71 (t,
															$CH_2 \cdot CH_3$), 8·85 (d, Me)
M	Me	H	C	17	123—124	64·8	7·75	6·15	64·6	7·6	6·3	223	1703 [b]	303	4·68 (s, =CH), 6·30 (m, CH and
													1625	(27,300)	$CH_2 \cdot O \cdot CH_2$), 6·72 (m, $CH_2 \cdot$
													1573		$N \cdot CH_2$), 7·68br (s, COMe and
															$[CH_2]_2$)
Py	Me	H	B	31	53—54	69·3	8·15	7·0	69·6	8·2	6·8	207	1715 [b]	305	4·86 (s, =CH), 6·34 (m, CH), 6·70
			C	6									1553	(28,100)	(m, $CH_2 \cdot N \cdot CH_2$), 7·69 (s,
															COMe), 7·75 (s, $[CH_2]_2$), 8·03
															(m, $[CH_2]_2$)
P	Me	H	B	21	Oil	70·3	9·1	5·9	70·6	8·6	6·3	221	1710 [c]	307	4·60 (s, =CH), 6·33 (m, CH), 6·70
													1603	(29,500)	(m, $CH_2 \cdot N \cdot CH_2$), 7·70 (s,
													1550		COMe), 7·74 (s, $[CH_2]_2$), 8·35
															(m, $[CH_2]_2$)
M	Ph	H	C	22	139—140	71·4	6·95	4·7	71·6	6·7	4·9	285	1673 [b]	301	1·92 and 2·43 (m, Ph), 4·52 (s,
													1617	(27,200)	=CH), 5·24 (m, CH), 6·33 (m,
													1570		$CH_2 \cdot O \cdot CH_2$), 6·74 (m, $CH_2 \cdot$
															$N \cdot CH_2$), 7·72 (m, $[CH_2]_2$)
Py	Ph	H	B	29	208—210	75·5	7·2	4·7	75·8	7·1	5·2	269	1678 [b]	301	1·9 and 2·38 (m, Ph), 4·52 (s,
													1613	(31,100)	=CH), 5·24 (m, CH), 6·74 (m,
													1554		$CH_2 \cdot N \cdot CH_2$), 7·69 (m, $[CH_2]_2$),
															8·08 (m, $[CH_2]_2$)
P	Ph	H	B	33	148—149	76·3	7·55	4·7	76·5	7·4	5·0	283	1673 [b]	304	1·92 and 2·39 (m, Ph), 4·46 (s,
			C	12·5									1623	(31,250)	=CH), 5·35 (m, CH), 6·74 (m,
													1563		$CH_2 \cdot N \cdot CH_2$), 7·69 (m, $[CH_2]_2$),
															8·39 (m, $[CH_2]_3$)

[a] See Table 1.   [b] Nujol.   [c] Liquid film.

τ 7·87 due to the two methyl groups, suggesting a symmetrical structure [*viz.* (VIII)], this accidental equivalence was not observed for a solution in deuterio-chloroform (τ 7·68 and 7·82; Table 3). Similarly the accidental equivalence of the two aromatic protons for solutions in carbon tetrachloride, perdeuteriobenzene, and deuteriochloroform (Table 3) was not observed for a solution in deuteriopyridine. Two singlets (τ 3·13 and 3·23), broadened by *meta-* and benzylic coupling, were

³ (*a*) E. S. Waight and R. L. Erskine, 'Steric Effects in Conjugated Systems,' ed. G. W. Gray, Butterworths, London, 1958, ch. 7; (*b*) A. E. Lutskii and V. V. Dorofeev, *Zhur. obshchei Khim.*, 1957, **27**, 1059, 1064.

the intensity of the low-field aromatic proton signal only (at τ 3·13). This rules out structure (VIII) in

TABLE 3

Assignments of the [1]H n.m.r. signals (τ values) of 2',4'-dimethyl-6'-morpholinoacetophenone (VII) (60 MHz)

Solvent	3'- and 5'-H	$CH_2 \cdot O \cdot CH_2$	$CH_2 \cdot N \cdot CH_2$	COMe	2'- and 4'-Me
C_6D_6	3·4	6·46	7·29	7·63	7·87
$CDCl_3$	3·2	6·23	7·06	7·48	7·68, 7·82
CCl_4	3·30	6·34	7·16	7·60	7·72, 7·88
C_5D_5N	3·23, 3·13	6·26	7·11	7·45	7·74, 7·77

which a nuclear Overhauser effect on both aromatic proton signals should have been observed.

The formation of 2',4'-dimethyl-6'-morpholinoaceto-phenone, which is also formed by heating 4-morpholino-pent-3-en-2-one (IX) in benzene in the presence of toluene-p-sulphonic acid, can be rationalised as shown in the Scheme. *O*-Acylation or protonation (E = RCO

(R² = Me or Ph)

180°), were unsuccessful. No evidence for the formation of other acetophenones, by self-condensation of the other
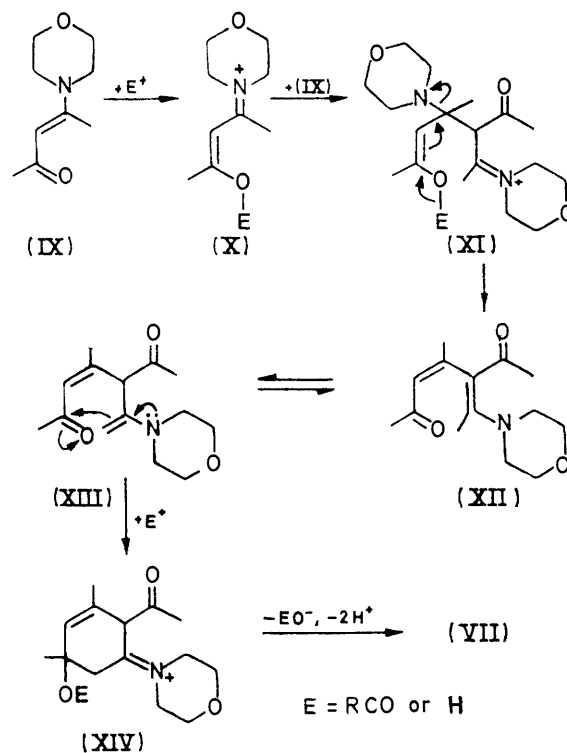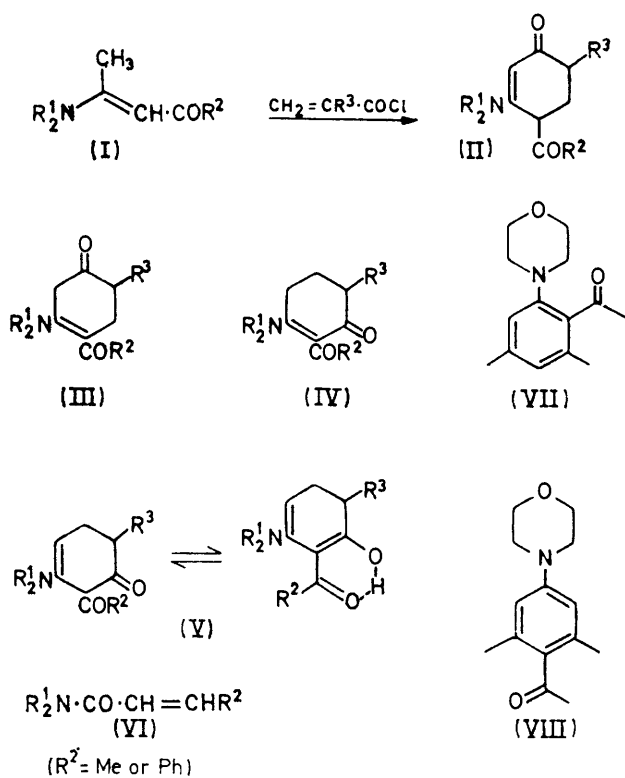
SCHEME

enamino-ketones and -esters used in these reactions with acryloyl chloride, has been observed.

or H, respectively) results in activation of the enamino-ketone to nucleophilic attack by a second molecule of enamine [(IX) ⟶ (XI); 1,4-addition]. Subsequent elimination of the amine residue, cyclisation onto the reformed carbonyl group, and aromatisation then led to the observed product [(XI) ⟶ (XII) ⇌ (XIII) ⟶ (XIV) ⟶ (VII)]. The acid-catalysed equilibration [(XII) ⇌ (XIII)] will be favoured by the reduced mesomeric stabilisation involving the nitrogen lone pair in (XII), owing to the severe steric interactions between the *cis*-oriented substituents on either side of the enamine double bond, in a planar conformation of (XII). Initial nucleophilic attack on the carbonyl group in (IX) by a second enamine molecule (1,2-addition), leading to the other isomer (VIII), does not appear to occur to any appreciable extent. Other examples of nucleophilic displacement of the amine residue in the reactions of tertiary enamino-ketones with Grignard reagents,[4] amines, hydroxylamine, hydrazines, and other nucleophiles,[5] have been reported. Attempts to increase the yield of compound (VII), by acid-catalysed self-condensation of 4-morpholinopent-3-en-2-one (IX) in various solvents (xylene, mesitylene, or aceto-nitrile) at the boil, or by the action of heat alone (at

EXPERIMENTAL

U.v. and i.r. spectra were determined with Unicam SP 800A and Perkin-Elmer 257 spectrophotometers, respectively, and the n.m.r. and mass spectra with Varian A60 and A.E.I. MS 12 instruments.

Preparation of Enamino-ketones and -esters.—A mixture of the 1,3-diketone or β-keto-ester, the secondary amine (in slight excess), and toluene-p-sulphonic acid (catalytic amount) was heated under reflux in benzene for 48 h; the water was removed initially by means of a Dean–Stark separator and then by a molecular sieve. The solvent was evaporated off and the product obtained by distillation (if a liquid) or recrystallisation (if a solid) of the residue. Preparative and spectral data are summarised in Table 1.

Synthesis of Cyclohex-2-en-1-ones.—*Method* (*A*). The enamino-ketone or -ester (0·01 mol) was dissolved in dry benzene (30 ml) and heated under reflux. The αβ-un-saturated acid chloride (0·01 mol) in dry benzene (25 ml) was then added dropwise during 1 h to the boiling solution. The mixture was heated under reflux until evolution of hydrogen chloride had ceased (*ca.* 48—72 h). The solvent was evaporated off *in vacuo* and the residual oil purified by preparative t.l.c. on silica in chloroform–acetone (1 : 1).

Method (*B*). This differed from method (A) in that the enamino-ketone or -ester (0·01 mol) was dissolved in a larger volume of benzene (100 ml) and the acid chloride

[4] G. Schroll, H. J. Jakobsen, and S.-O. Lawesson, *Rec. Trav. chim.*, 1965, **84**, 597.

[5] J. C. Martin, K. R. Barton, P. G. Gott, and R. H. Meen, *J. Org. Chem.*, 1966, **31**, 943.

(0·01 mol) in benzene (30 ml) was added during a longer period (5 h) to the enamine solution at the boil.

Method (C). The enamino-ketone or -ester (0·01 mol) was dissolved in benzene (10 ml) and the acid chloride (0·01 mol) in benzene (10 ml) was added during 1 h at ambient temperature. The mixture was stirred for 30 min, an excess of dry triethylamine (4 ml) was added, and the product was heated under reflux for 30 min. The mixture was allowed to cool with stirring overnight, the triethyl-amine hydrochloride was filtered off, the solution was evaporated *in vacuo*, and the product was isolated as in method (A).

Preparative, analytical, and spectral data are summarised in Table 2.

2′,4′-*Dimethyl*-6′-*morpholinoacetophenone*.—The reaction of acryloyl chloride with 4-morpholinopent-3-en-2-one under the conditions of method (A) gave 4-acetyl-3-morpholino-cyclohex-2-en-1-one (Table 2) and 2′,4′-*dimethyl*-6′-*morpholinoacetophenone*, isolated as a solid by preparative t.l.c.

[benzene–acetone (95 : 5)] in 18% yield; m.p. 62—63° [from light petroleum (b.p. 60—80°)–benzene] (Found: C, 72·5; H, 8·1; N, 5·7%; M^+, 233. $C_{14}H_{19}NO_2$ requires C, 72·1; H, 8·2; N, 6·0%; M, 233), $\nu_{max.}$ (Nujol) 1695, 1604, and 1573 cm^{-1}. U.v. and ^{1}H n.m.r. data are given in the Discussion section and Table 3. The yield was increased slightly (to 21%) by changing the molar ratio of enamine to acid chloride to 2 : 1. The same product was formed, in low yield, by heating 4-morpholinopent-3-en-2-one in a variety of solvents (benzene, xylene, mesitylene, or acetonitrile) under reflux, in the presence of toluene-*p*-sulphonic acid for 96 h.